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09/694,758	10/23/2000	Shukti Chakravarti	CWV-001.01	7408

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EXAMINER	
PONNALURI, PADMASHRI	
ART UNIT	**PAPER NUMBER**
1639	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/694,758	Applicant(s) Chakravarti
	Examiner Padmashri Ponnaluri	Art Unit 1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 6, 2003*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *5-7 and 19-29* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *5-7 and 19-29* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 14
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The amendment B, filed on 2/6/03 has been fully considered and entered into the application.

2. Claims 5-6 have been amended and new claims 19-29 have been added by the amendment B, filed on 2/6/03. NOTE that applicants amended claim methods use a library of genes (based on at least 5 genes) expression, not an assay of screening a single gene expression as originally claimed.

3. Claims 5-7 and 19-29 are currently pending in this application.

4. The new oath/declaration filed on 2/6/03 has been considered and entered into the application.

5. The rejection of claims 5-7 over Puolakkaiene et al has been withdrawn in view of amendments to the claims.

New Rejections Necessitated by the Amendments

6. Claims 5-7 and new claims 19-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The instant claims briefly recite a method for determining the phenotype of a test cell, comprising detecting the differential expression relative to normal cell of at least 5 different genes shown in table 1.

The specification description is directed to a method comprising I) generating a first library of nucleic acid probes representative of genes expressed by intestinal tissue of an animal without apparent risks or symptoms of IBD; ii) generating a second library of nucleic acid probes representative of genes expressed by intestinal tissue of animal which has symptoms of IBD; iii) identifying the genes up or down regulated, and the method is useful in determining a phenotype of a cell. Thus, genes involved in up or down regulated in IBD condition have to be identified and probes of these genes are generated and formed micro arrays of the generated probes in identifying phenotype of a cell as claimed.

The specification disclosure does not recite or has given examples of the identified up or down regulated IBD genes or the probes generated from the genes identified or the micro arrays. The specification discloses that the libraries of nucleic acid probes (at least 5 genes refers to a library) for indexing the level of expression of one or more IBD genes. And the IBD probes will be isolated nucleic acids comprising a nucleotide sequence which hybridizes under stringent conditions to a sequence of table 1 (see page 3). Further the specification discloses that the nucleic acid probes for indexing the level of expression of IBD genes are nucleic acid sequences (12-40 consecutive nucleic acids) correspond to the IBD gene set. Thus, the IBD gene set in Table 1 is not directly used in the claimed invention. Nucleic acid sequences identical or which correspond to the nucleic acid sequences of the IBD gene set in Table 1 has to be determined such that the identified nucleic acid sequences can be used as probes in the claimed method.

The claimed method depends upon identifying nucleic acid sequence probes after hybridizing with known IBD gene set, and prepare micro arrays of using the identified probes and use the array in the claimed method. The specification does not disclose the nucleic acid sequences which are identified after hybridizing with the known IBD gene set. Without knowing the probes (or nucleic acid sequences) it is impossible to practice the claimed method. Without the probes (or nucleic acid sequences) the claimed invention is more theoretical tan real.

The specification disclosure is narrative and based on hypothetical method. The specification does not include any working examples or experiments in which the genes involved in up- pr down-regulated in intestinal tissue of patients are used in the method of determining phenotype or to assess a patient's risk of having or developing an inflammatory bowel disease. Thus, applicants are not in possession of the genes involved in the IBD.

With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)].

Thus, it requires a representative sample of compounds and/or a showing of sufficient identifying characteristics; to demonstrate possession of the claimed generic(s).

In the present instance, the claimed invention contains no identifying characteristics regarding the probes used in the claimed method.

Additionally, the specification in absence of working examples is clearly not representative of the presently claimed invention.

7.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 5-7 and 19-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims are vague and indefinite by reciting 'differential expression relative to a normal cell'. The specification does not disclose what is considered as a normal cell. Does applicants mean the normal cell is from a tissue culture or the normal cell is from a healthy individual, and the term is 'normal' is a relative term. Is the cell 'normal' compare to a specific cell or condition or expression of specific genes. Applicants are requested to clarify.

Claims recite 'phenotype of a test cell', it is not clear what does applicants mean by phenotype of a test cell. What is considered as phenotype of a test cell is not clear. And further the claims recite 'presence or absence of differential expression', it is not clear what is differential expression. Ad in later dependent claims recite that the differential expression is a factor of two.

The factor applicants referring to (factor of two) is very basal, and even in different normal cells the differential expression which differ by a factor of two is normal, which would not be indicative of any disease condition.

Claims 5, 28 and 29 recite the limitation "the phenotype" . There is insufficient antecedent basis for this limitation in the claim.

Claims 5-7 and 19-29 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the instant claimed method does not recite how or which phenotype of the cell is determined; and how the phenotype is detected and method of identifying the differential expression. The claims do not recite how the assay is performed. Further the instant claim is drawn for determining the phenotype of a test cell by detecting the presence or absence of differential expression. It is not clear how detecting the differential gene expression is related to the phenotype of the test cell.

Claim 5 is vague and indefinite by reciting ' phenotype of a cell', it is not clear what does applicants mean by phenotype of a cell. Does applicants mean that physical changes of a cell or the method uses external markers, etc., it is not clear. Applicants are requested to clarify.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 5-7 and 19-21, 24-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Alexander et al (Digestive Diseases and Sciences, vol. 41, No. 4, April 1996, pp 660-669) (reference provided by applicants in PTO 1449, filed on 5/16/02).

The instant claims briefly recite a method for determining the phenotype of a test cell, comprising detecting the differential expression relative to normal cell of at least 5 different genes (refers to a library of genes) shown in table 1.

Alexander et al disclose a method to determine altered expression of protooncogenes (cell cycle related genes) in patients with inflammatory bowel disease (IBD). The reference assayed transcripts of 15 protooncogenes (refer to other IBD genes of the instant claims) in colonic epithelial cells of IBD patients and controls (refers to the normal cells of the instant claims) (i.e., see abstract). The reference discloses that increased levels (refers to the differential expression of the instant claim) of soluble mediators (e.g. Leukotrienes, prostaglandins) (refer to other IBD genes of the instant claims) of inflammation as well of the cells of immune system have been found to be present in the intestinal mucosa and submucosa of IBD patients (i.e., see page 660, last paragraph bridging first paragraph in page 661). The reference discloses expression of transcripts of eight growth factor receptor related genes in colonic epithelial cells of IBD patients and controls (i.e., see left column in page 661). The reference discloses that increased expression of PDGF-R-β mRNA involved epithelium, compared to matched uninvolved epithelium, and the

transcript level of this gene, as well three other growth factors was considerably higher in colonic epithelial cells of IBD patients (i.e., see page 661).

The reference discloses that prior to determining whether there were any differences between IBD samples and controls in their relative expression of protooncogene transcripts, it was necessary to determine the degree of expression of each of the genes in normal colon epithelial cells (i.e., see page 662, right column, section under results). The reference discloses that hybridization of radio labeled probes to slot blots of RNA extracted from normal epithelial cells of patients rejected for diverticulitis and sporadic cancer revealed that transcripts of five protooncogenes were abundant in these samples (refers to a method of selecting genes involved in IBD). The reference discloses that the level of expression of *c-fos* in the involved IBD samples was about twofold higher than in the uninvolved IBD samples (refers to instant claim 6). Thus, the reference clearly anticipates the claimed invention.

11. Claims 5-7 and 19-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Dieckgraefe et al (Digestive Disease and Sciences, 114, No.4, G3954, April 1998) (reference provided by applicants in the PTO 1449 filed on 5/16/02).

Dieckgraefe et al disclose a method for identifying gene expressed in IBD. The reference have used GeneChip expression monitoring system to examine mucosal gene expression in ulcerative colitis, Crohns' colitis, and both in inflamed and non-inflamed non IBD specimens. The reference's aim was to identify gene markers differentially expressed in Crohns' disease and ulcerative colitis; identify genotype associated with disease subsets and characteristics. The

reference in methods disclose RNA isolated from the mucosa of colonic reaction specimens was used to generate hybridization probes, and light directed solid-phase combinatorial chemistry was used to generate oligonucleotide probe array. The reference in results section discloses that dramatic changes were seen in the expression of wide range of genes, and genes were identified which appear to be specific markers for the specific diagnosis, disease activity and specific feature of histology. Thus, the reference clearly anticipates the claimed invention.

Response to Arguments

12. Applicant's arguments filed on 2/6/03 regarding the written description rejection, have been fully considered but they are not persuasive.

Applicants assert that the specification provides sufficient written description for the full scope of the invention. In particular, Table 1 of the specification recites more than 140 genes which are differentially expressed and can be useful in the claimed methods for determining the phenotype of a test cell. Furthermore, table 1 identifies the individual genes with their Gene Bank accession number, thus placing those skilled in the art in possession of the relevant gene sequences. Applicants argue that the accession number is a 'precise definition' that is sufficient to distinguish each of the referenced nucleic acid sequences from other sequences.

Applicants arguments and assertions have been fully considered and entered. However, the arguments and assertions are not persuasive because the specification recites 140 genes related to

IBD, and their Gene Bank accession numbers. However, the claimed invention is not claiming the genes from the list of 140 genes of table 1. The instant invention is drawn to a method of determining the phenotype of a test cell compare to a normal cell by detecting differential expression at least 5 genes from table 1. In the claimed method the genes of the table 1 are not used. The claimed method uses probes (nucleic acid sequences) which are similar or identical or complementary to the genes of table 1. Thus, the probes have to be identified or prepared which are identical or complementary to the genes in table 1, and arrange or prepare in array format such the probes are useful in the claimed method. Applicants have not shown as in possession of the probes useful in the claimed method at the time of filing of the claimed invention.

14. Applicant's arguments filed on 2/6/03 regarding the rejections of claims under 35 U. S. C. , 112, second paragraph have been fully considered but they are not persuasive.

A) Applicants argue that 'phenotype of a cell' is well known in the art to mean anything that is part of observable structure, function or behavior of a living organism. However, the definition of 'phenotype' is known, it is not clear what observable phenotype is being determined in the claimed method. And it is interpreted that the cells in the instant claimed method are not present in a living organism, i.e., the claimed method is not drawn to in vivo method, such that behavior of the living organism is observed. Thus, it is not clear what phenotype is being detected in the claimed method. The specification does not have a list of phenotypes detectable or detected by the claimed method. If applicants mean that the gene expression is indicative of the phenotype, but the claimed method does not recite how the gene expression is detected.

15. Applicant's arguments filed on 2/6/03 regarding the art rejection of claims over Puolakkainen et al have been fully considered. Applicants arguments are moot in view of withdrawal of rejection. However, examiner would like to bring to the attention of applicants that the instant claimed method does not detect unknown phenotype of test cell as in applicants arguments, and the instant claims are drawn to determining the differential expression of genes which is indicative of phenotype.

16. Applicant's arguments filed on 2/6/03 regarding the art rejection of claims over Alexander et al have been fully considered but are not persuasive. Applicants argue that Alexander et al do not teach each and every element of the claims. Applicants argue that Alexander et al does not teach determining the phenotype of a cell by detecting the presence or absence of differential expression as required claimed methods.

Applicants arguments have been considered but are not persuasive, because Alexander et al disclose a method to determine altered expression of protooncogenes. The reference discloses that increased expression of PDGF-R-β mRNA involved epithelium, compared to matched uninvolved epithelium (refers to normal cells) and the transcript level of this gene, as well three other growth factors was considerably higher in colonic epithelial cells of IBD patients (i.e., see page 661). Thus Alexander et al teach a method of determining differential expression of genes involved in IBD compare to normal cells.

Applicants arguments support that the reference method teaches detecting differential expression of IBD genes by stating that Alexander et al characterize expression of several

protooncogenes, including H-ras, c-myc, c-fos, c-jun, junB, -myc, c-abl, c-yes and p53 in colonic epithelial cells of patients and normal cells (see pages 16-17 of the response).

17. Applicants further argue that Alexander et al characterize up or down regulation of several oncogenes in cells of a **known phenotype**. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., unknown phenotype of test cells) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

(Fed. Cir. 1993). The instant claims do not recite 'known phenotype' in the instant claims, and further the claims do not even recite how detecting the differential expression is related to the phenotype of the test cells. The instant claims have been interpreted that the method of determining the phenotype of test cell is determining the differential expression of the cells.

Applicants further argue that Alexander et al do not teach detecting the presence or absence of differential expression if at least 5 genes shown in Table 1. Applicants arguments are not persuasive, since Alexander et al disclose differential expression different genes which would read on at least 5 genes of the instant claims.

18. Applicant's arguments filed on 2/6/03 regarding the art rejection of claims over Dieckgraefe et al have been fully considered but are not persuasive. Applicants argue that Dieckgraefe et al do not describe determining the phenotype of a test cell of **unknown phenotype** by detecting the presence or absence of differential expression of a gene relative to an normal cell. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., unkown phenotype of test cells) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The instant claims do not recite 'known phenotype' in the instant claims, and further the claims do not even recite how detecting the differential expression is related to the phenotype of the test cells. In the

absence of guidance the instant claims have been interpreted that the method of determining the phenotype of test cell is determining the differential expression of the cells.

19. No claims are allowed.

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to P. Ponnaluri whose telephone number is (703) 305-3884. The examiner is

on ***Increased Flex Schedule*** and can normally be reached on Monday to Friday from 7.00 AM to 3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

P. Ponnaluri
Primary Examiner
Technology Center 1600
Art Unit 1639
13 May 2003

PADMASHRI PONNALURI
PRIMARY EXAMINER